A Discrete Events Delay Differential System Model for Transmission of Vancomycin-Resistant Enterococcus (VRE) in Hospitals

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Abstract

Surveillance data from an oncology hospital unit on Vancomycin-resistant Enterococcus (VRE), one of the most prevalent and dangerous pathogens involved in hospital infections, is used to motivate possibilities of modeling nosocomial infection dynamics. This is done in the context of hospital monitoring and isolation procedures as a prelude to the evaluation and improved design of control measures. A discrete event delay differential equation model in conjunction with statistical computational methods is formulated to estimate key population-level nosocomial transmission parameters and isolation procedures. This framework is used to test the surveillance data's usefulness in model validation. In the process of model calibration we discovered significant irregularities in the available surveillance data; these irregularities are most likely the result of the data observational recording-process as well as those in the isolation procedures. Efforts to fit data within our highly flexible dynamic-modeling framework suggest that clinical-trial level surveillance data is needed if one is to successfully develop quantitative models for disease transmission and intervention. It is concluded that typical "cold" data sets typically encountered in biological/sociological quantitative modeling efforts may be inadequate for support of serious model development.

Key Words: Delay equations, discrete events, nosocomial infection dynamics, surveillance data, inverse problems, parameter estimation.

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1 Introduction

One of the more difficult endeavors in inverse problems is the development and evaluation (validation) of mathematical and statistical models with so-called "cold data". This data, often routinely available in sociological and biological investigations, which are quantitative observations (often mixed with anecdotal information), are typically collected with no formal quantitative modeling anticipated. Rather, the collectors have in mind some vague idea of recording their observations in hope that this data will somehow be useful in understanding (often at the dynamical or longitudinal level) the process (biological, physical, sociological, etc.) of interest to them. An important contribution that inverse problem investigators can make is to understand when a data set is or is not suitable for model validation. Numerous quantitative modeling tools (mathematical and statistical) are available to aid in this effort; a brief review of some of these can be found in [9, 11, 12, 13]-see also [16]. In this paper we present a detailed example of a modeling attempt based on "data" from an isolation process at hospitals in the US. In [31] we used hospital based Vancomycin-resistant Enterococcus (VRE) disease data to motivate development of the most "natural" dynamics model. This entailed a stochastic Markov process model for transition between compartments consisting of healthy (uncolonized), unhealthy (colonized) patients in the hospital population and colonized patients in isolation. The use of data with such small population stochastic models in parameter estimation efforts is difficult. In [31] we presented a methodology for using the corresponding limit (in large population) mean (sample path averages) population dynamic model containing the transition parameters to estimate the transition probabilities in the stochastic models. The emphasis in [31] was on methodology and little attention was given to efforts to further develop the models to obtain good fit to the experimental data. Here we focus on careful efforts to develop longitudinal models to describe the data as understood by hospital workers. In particular we develop models in attempts to include precise events as described in the data and reported by hospital workers in the data acquisition process. In these efforts we attempt to model the disease progression (the mathematical model) along with the data collection procedures (the statistical model) as faithfully as possible in an effort to decide if the "cold data" is useful in modeling attempts or is use of the data with precisely formulated mathematical and statistical models somehow fraught with fundamental difficulties, i.e., is it an "ill-posed problem" in and of itself? For example is the data collection itself flawed, resulting in such large variability that it is essentially unsuited for such modeling? If so, one should use experimental optimal design criteria and methodology [3, 11, 12, 17, 25, 26] to design specific experiments (i.e., data collection protocols) in support of the modeling process. Successful examples of such endeavors are given in [15, Chapter V, Sec. 6, 7] and more recently in [10].

We begin with the ordinary differential equation system for sample path averages suggested by the stochastic model of [31] and modify the model to include jump discontinuities and time delays (both scheduled) that are reported in detailed accounting of the hospital and data acquisition procedures. We then show how to reformulate the

corresponding delay system as an abstract evolution system in a hereditary space so that standard finite element type approximations are applicable. We then use known mathematical and statistical methodology for inverse problems to investigate the resulting problem in the context of the available data. We first give a summary of the pertinent facts underlying VRE infections and transmission in hospital settings.

2 VRE Background

Nosocomial, or hospital-acquired infections, the fourth cause of death [1] in the US, are evidence that hospitals provide not only medical care but also harbor pathogens that pose serious, often fatal, risks of infection, particularly to the young, the elderly, and immune-compromised individuals. Infection-control measures aimed at reducing their impact are being implemented with various degrees of efficiency at US hospitals.

Hospitals and health care professionals are committed to improve the health of their patients. However, there are risks associated with the provision of health care with one of the most important being the acquisition of infections at hospitals. The Centers for Disease Control and Prevention (CDC) estimates that 5% to 10% of patients, or more than two million patients each year will get an infection while in a United States hospital with about $90,000$ of them dying from such infections [21]. These hospitals-acquired infections or nosocomial infections are infections not present or incubating in a patient at the time of admission to a hospital or health care facility. Three decades ago infection-control measures were put in place to control antibiotic-resistant nosocomial infections and yet these infections have continued to increase. Multidrug-resistant pathogens have become increasingly problematic, especially in the critical care setting.

Most of the nosocomial infections are primarily caused by antibiotic resistant pathogens, such as Vancomycin-resistant Enterococcus (VRE). VRE is the group of bacterial species [18] of the genus enterococcus that is resistant to the antibiotic vancomycin and it can be found in the digestive/gastrointestinal, urinary-tracts, surgical-incision, and blood-stream sites.

The duration of colonization could last from weeks to months [20]. The factors most associated in predisposing VRE colonization to patients includes: a compromised immune system or nutritional status, the use of catheters (such as urinary or central venous), co-morbidities (e.g., diabetes, renal insufficiency, cancer), length of stay in the hospital, inadequate infection control practice among health care workers (HCW), and prolonged antibiotic used (> 10 days). Hence VRE patients admitted in hospital units such as intensive care and oncology have a greater colonization risk.

Transmission of VRE can occur through contact with colonized or infected individuals (although, there are cases in which VRE acquisition may arise from the patient's own gut flora). The most frequent form of transmission is by contact, categorized as direct-contact transmission or indirect-contact transmission. Direct-contact transmission involves direct physical contact (mostly hands) between a susceptible host and a colonized agent. Indirect-contact transmission involves contact between a susceptible host and a contaminated institutional environment, that includes health care workers

(human vectors).

The CDC Hospital Infection Control Program [22] encourages hospitals to develop their own institution-specific interventions plans that should stress: prudent vancomycin use by clinicians, hospital staff education regarding vancomycin resistance, early detection and prompt reporting of vancomycin resistance in enterococci by the hospital microbiology laboratory, and immediate implementation of appropriate infection control measures (such as isolation) to prevent person-to-person VRE transmission. Isolation procedures consist mostly of frequent hand washing which is considered the single most important control measure.

Deterministic and stochastic models have made substantial contributions to our understanding of the epidemiological dynamic of infections [2, 19, 27]. Hence, they have been valuable tools to predict and explain the epidemiology of nosocomial infections. Many of the models developed to describe the transmission of nosocomial infection in a health care setting have been based on the Ross-Macdonald model [32] where the transmission of pathogens in health care settings considers health care workers as vectors and patients as hosts [4, 23, 29, 30, 34]. These models have been used in attempts to explain the spread of infections, specifically by investigations of the impact of infection control measures such as patient isolation, hand-washing, and bacterial-control among others.

In this paper we discuss mathematical models for the transmission of VRE in a hospital unit. The development of these models is based on the epidemiological knowledge of VRE in a setting that allows for the implementation of infection control measures in hospitals. We focus on the connection of these models with unpublished VRE surveillance data from an oncology unit in order to estimate some of the parameters that govern the underlying transmission infection dynamics. The usefulness of our new flexible modeling framework for the transmission dynamics of nosocomial infections like VRE was first evaluated using synthetic noisy data and then tested against the available data. Our conclusions for this particular data set are then detailed.

3 Surveillance data

The motivating surveillance data is from an oncology unit, obtained from the VRE Infection Control database of the Department of Quality Improvement Support Service of Yale-New Haven Hospital. Data reports on the number of VRE cases occurred on admission (including patients transferred), the patients' length of stay, the daily number of patients in isolation due to VRE colonization, the compliance of swab culture administered on admission, and the health care worker contacts precautions compliance. Data collection occurred during the period of January 2005 to January 2007 with a mean number of 31 in-patients per day (with a total of 37 beds).

Ward protocol required rectal swabbing of all patients on admission, and once a week thereafter (every Tuesday) for VRE surveillance. Compliance was not 100%, as the mean percentage of swab cultures taken on admitted patients per day was 77%. Swab-test results usually were returned 48 hours after admission. If a patient tested VRE positive, he/she was isolated. The isolation procedure consisted of contact precautions by the

use of gowns, gloves, and the location of a patient to a single room or to a room with another patient who was also VRE positive. If a readmission patient had a positive VRE culture in the past, he/she did not receive the rectal swab on admission and was isolated immediately. The isolation report was performed on weekdays (no weekends or holidays). The mean number of isolated VRE colonized patients per day was 9.39 (std=2.90) patients.

4 VRE epidemic model

We consider a deterministic continuous time compartmental model in which patients in a hospital unit are classified as either uncolonized $U(t)$, VRE colonized through admission $C_1(t)$, VRE colonized during hospital stay $C_2(t)$, and VRE colonized patients in isolation $J(t)$, as depicted in the compartmental schematic of Figure 1. (A related Markov Chain stochastic model is presented in [31]).

We assume homogenous mixing, that is, each patient is considered equally likely to be in contact with a health care worker in any time interval, equally likely to be VRE colonized, and, if VRE colonized at a given time, equally likely to transmit the pathogen at a given time. Patients are admitted to the hospital unit at a rate Λ per day and some fraction m are already VRE colonized. Therefore, VRE colonized patients through admission (C_1) enter the hospital at a rate $m\Lambda$ and uncolonized patients enter the hospital at a rate $(1-m)\Lambda$. VRE colonized patients ($C_1, C_2,$ and J) are discharged at a different rate from uncolonized patients. Uncolonized patients become VRE colonized at a rate proportional to the prevalence of patients carrying the bacteria. It is assumed that an average patient in the population makes βN effective contacts (i.e., contact sufficient to lead to VRE colonization) with other patients per unit time through health care workers, where N is the total population size. Since the probability is U/N that a random contact by a VRE colonized patient is with an uncolonized patient, the number of new colonization in unit time per infective is $(\beta N)(U/N)$. This yields a rate of new VRE colonization $(\beta N)(U/N)\ [C_1+C_2+(1-\gamma)J] = \beta U[C_1+C_2+(1-\gamma)J]$. The hand-hygiene policy applied to health care workers on VRE colonized patients in isolation reduces infectivity by a factor of γ $(0 < \gamma < 1)$. This assumption means that isolated VRE colonized patients make fewer contacts than regular patients, so transmission of the bacteria by these isolated members has an infectivity factor $(1-\gamma)$. It is assumed VRE colonization periods last from weeks to months. In addition, because spontaneous decolonization occurs infrequently, clearance of the bacteria is not considered in the model. VRE colonized patients are not treated for VRE and all patients on admission are swab tested for VRE. A waiting time of two days for the results of the swab-test cultures is assumed for all patients in any time period. After results are returned, VRE colonized patients are moved into isolation (see the next section for the derivation of isolation rates). As a simplification, we assume that the total number of patients remains fixed (i.e., overall admission rate equals overall discharge rate, $\Lambda = \mu_1 U + \mu_2(C_1 + C_2 + J)$), and VRE colonization confers no additional mortality. Finally, the total population of patients can be written as $N = U + C_1 + C_2 + J$.

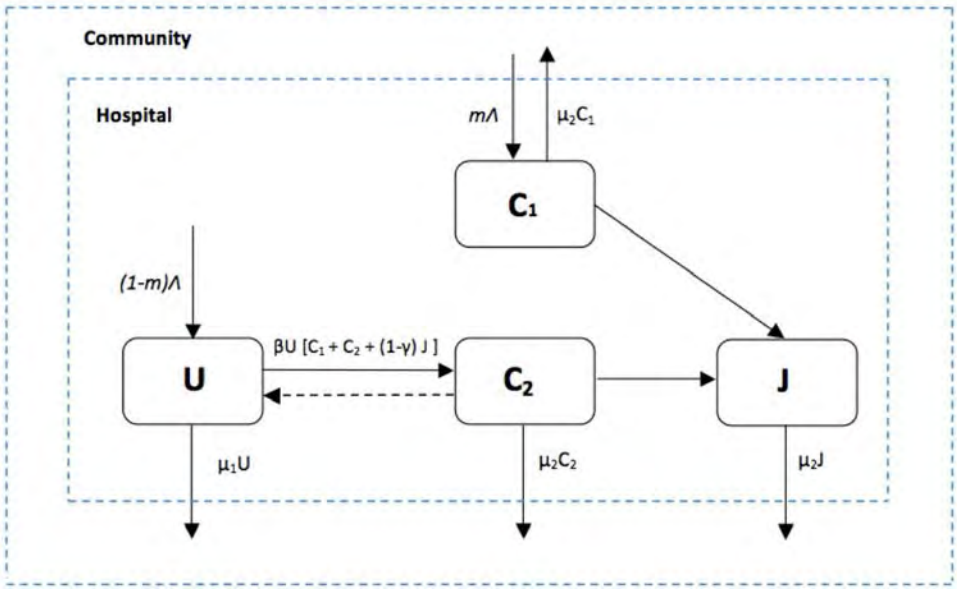


Figure 1: VRE compartmental model

A description of the variables and parameters used in our model are given in Table 1, and the model equations (which are derived in the next section) are the given by

$$\begin{aligned}
\frac{dC_1(t)}{dt} &= m\{\mu_1 N + (\mu_2 - \mu_1)[C_1(t) + C_2(t) + J(t)]\} \\
&- me^{-2\mu_2}\{\mu_1 N + (\mu_2 - \mu_1)[C_1(t-2) + C_2(t-2) + J(t-2)]\} \\
&- \mu_2 C_1(t) \\
\frac{dC_2(t)}{dt} &= \beta\{N - [C_1(t) + C_2(t) + J(t)]\}[C_1(t) + C_2(t) + (1-\gamma)J(t)] \\
&- \mu_2 C_2(t), \quad \text{for } t_i < t \leq t_{i+1} \\
C_2(t_{i+1}^+) &= C_2(t_{i+1}^-) - C_2(t_{i+1} - 2)e^{-2\mu_2} \\
\frac{dJ(t)}{dt} &= me^{-2\mu_2}\{\mu_1 N + (\mu_2 - \mu_1)[C_1(t-2) + C_2(t-2) + J(t-2)]\} \\
&- \mu_2 J(t), \quad \text{for } t_i < t \leq t_{i+1} \\
J(t_{i+1}^+) &= J(t_{i+1}^-) + C_2(t_{i+1} - 2)e^{-2\mu_2}
\end{aligned} \tag{1}$$

with initial conditions: $C_1(0) = C_{01}$, $C_2(0) = C_{02}$, $J(0) = J_0$, and a trajectory of the solution in the past: $C_1(\theta) = \Gamma(\theta)$, $C_2(\theta) = \Psi(\theta)$, $J(\theta) = \Omega(\theta)$ for $\theta \in [-2, 0)$.

Table 1: Description and units for model parameters and varaibles

Variables	Description	Units
$U(t)$	Number of uncolonized patients	Individuals
$C_1(t)$	Number of VRE colonized patients through admission	Individuals
$C_2(t)$	Number of VRE colonized patients during hospital stay	Individuals
$J(t)$	Number of VRE colonized patients in isolation	Individuals
Parameters	**Description**	**Units**
Λ	Patients admission rate	Individuals/day
m	VRE colonized patients on admission rate	Dimensionless
β	Effective contact rate	1/day
γ	HCW hand hygiene compliance rate	Dimensionless
μ_1	Uncolonized patients discharged rate	1/day
μ_2	VRE colonized patients discharged rate	1/day

4.1 Brief derivation of the model

The rate of change in the total population of C_1's can be modeled by considering the rate of admission to this compartment minus the rate at which C_1's are isolated and minus the rate at which C_1's are discharged before isolation. It is assumed that swab cultures are administered to every patient that is admitted (100% swab compliance) and that it takes two days for the test results to be returned. Therefore, two days after a colonized patient has been admitted, he/she will be isolated if he/she is not discharged over the waiting period of two days. Thus, the isolation rate of VRE colonized patients tested on admission depends on the past history of these patients. Since $m\Lambda(t)$ is the admission rate of VRE colonized patients, then $m\Lambda(t-2)$ is the rate at which the C_1's were admitted at time $t-2$. Some of those admitted at time $t-2$ may be discharged at a rate μ_2 before being isolated over the period of two days. Thus, we need to find the fraction of those admitted at time $t-2$ that are still admitted two days after.

We consider the "cohort" of patients who were all admitted at $t=0$, denoted by $C_1(0)$. Let $C_1(2)$ denote the number of these who are still in C_1 class 2 days later. If patients leave C_1 class at the rate μ_2 per day, then

$$\frac{dC_1(t)}{dt} = -\mu_2 C_1(t) \tag{2}$$

with initial condition $C_1(0) = C_{01}$. Hence

$$\frac{C_1(2)}{C_1(0)} = e^{-2\mu_2} \tag{3}$$

denotes the fraction of individuals who were admitted at time $t = 0$ and who are still admitted at time $t = 2$. Thus, the rate of isolation of C_1's at time t by factoring in discharges over the period of two days is $m\Lambda(t-2)e^{-2\mu_2}$. Then, the dynamics of C_1's at time t is given by

$$\frac{dC_1(t)}{dt} = m\Lambda(t) - m\Lambda(t-2)e^{-2\mu_2} - \mu_2 C_1(t) \tag{4}$$

with initial condition $C_1(0) = C_{01}$. Consequently, the rate of change of isolated VRE colonized patients at time t can be modeled as

$$\frac{dJ(t)}{dt} = m\Lambda(t-2)e^{-2\mu_2} - \mu_2 J(t) \tag{5}$$

which is the rate of C_1's entering to J class minus the discharge rate in unit time and with initial condition $J(0) = J_0$.

The rate of change in the total population of C_2's can be modeled by considering the rate of new colonizations during hospital stay minus the rate at which C_2's are isolated and minus the rate at which C_2's are discharged before isolation. Weekly swab cultures were administered every Tuesday. Assuming that every patient is tested (100% compliance) with two days for the test results to be returned (sometime before health care worker's night shift), we can assume that VRE colonized patients in C_2 class will be moved into isolation every Thursday night. Hence, there is not a delay involved here but rather a jump discontinuity every Thursday.

We let t_i be a Thursday and t_{i+1} be the next Thursday. We can then expect a jump discontinuity in the number of patients in C_2 class as well as in the number of patients in J class at time t_{i+1}. If $C_2(t_{i+1}^+)$ represents the number of patients in C_2 after isolation, then

$$C_2(t_{i+1}^+) = C_2(t_{i+1}^-) - C_2(t_{i+1} - 2)e^{-2\mu_2}. \tag{6}$$

Here $C_2(t_{i+1} - 2)$ represents the number of patients in C_2 class that were tested on Tuesday and $e^{-2\mu_2}$ is the fraction of those $C_2(t_{i+1} - 2)$ that were not discharged over the period of two days before isolation (it follows from the same derivations as represented in (3)). This jump discontinuity in C_2 influences a jump in J defined as

$$J(t_{i+1}^+) - J(t_{i+1}^-) = C_2(t_{i+1} - 2)e^{-2\mu_2}. \tag{7}$$

The number of isolated patients after isolation, $J(t_{i+1}^+)$, can be determined by the number of patients in J class before isolation plus the number of patients in C_2 class that were isolated at time t_{i+1}. Therefore, the dynamics for compartment C_2 and J at time t for

$t_i < t \leq t_{i+1}$ are given by

$$\frac{dC_2(t)}{dt} = \beta U(t)\left[C_1(t) + C_2(t) + (1-\gamma)J(t)\right] - \mu_2 C_2(t) \quad (8)$$

$$\frac{dJ(t)}{dt} = m\Lambda(t-2)e^{-2\mu_2} - \mu_2 J(t), \quad (9)$$

with initial condition $C_2(0) = C_{02}$, $J(0) = J_0$. The rate of change for C_2 class is modeled by the rate of new colonizations minus the rate of discharged in unit time. The rate of change of J class is modeled by the rate of C_1's entering J minus the discharge rate in unit time.

Finally, we assume the overall admission rate equal to the overall discharge rate, i.e., $\Lambda(t) = \mu_1 U(t) + \mu_2[C_1(t) + C_2(t) + J(t)]$. In order to keep the overall rate of admission equal to the overall rate of discharge, we replace $U(t) = N - [C_1(t) + C_2(t) + J(t)]$ obtaining the system of equations given in (1).

4.2 Parameters estimated directly form the surveillance data

Infection control measures were implemented in the form of health care worker hand-hygiene before and after patients contact by the use of gloves and gowns, and washing of hands. For this study we consider the health care worker before patient contact compliance of 57.56% as a better estimator for the parameter γ. In the oncology unit VRE colonized patients had a mean length of stay of 13.15 days (std=18.28) compared with 6.27 (std=6.80) for the uncolonized patients. These means are statistically significantly different (p-value < 0.0001), supporting the assumption of different discharge rates. Hence, we take $1/\mu_1 = 6.27$ and $1/\mu_2 = 13.15$ giving $\mu_1 = 0.16$ and $\mu_2 = 0.08$.

In an attempt to estimate the fraction m of patients that are colonized on admission, we found inconsistencies in the reported prevalence of VRE on admission (the summaries of admitted patients did not match the actual data). In estimating the initial conditions (C_{01}, C_{02}, J_0) from the data reported on the first day of data collection (January 3, 2005), only the number of VRE colonized patients in isolation is reported. Hence, the initial conditions for C_1 and C_2 classes cannot be easily estimated. Another parameter that is of interest and can not be estimated directly from the data is the VRE transmission rate β. As a result, the fraction of patients that are colonized on admission and the transmission rate are estimated using inverse problem methodology. In Table 2 we present the estimated and assumed values of the parameters and initial conditions required for inverse problem calculations.

5 Numerical implementation

The solutions to the system (1) can be simulated using an algorithm developed by Banks and Kappel [14] and extended for nonlinear systems [5, 6, 28] (see also [7, 8] for applications of this algorithm). The idea behind the algorithm is to first represent the system as an infinite dimensional abstract evolution equation (AEE) and then consider

Table 2: Parameters and initial conditions values (values assumed are used for optimization purposes)

Initial Conditions	Oncology Unit (N=37)	Units	Source
$[C_{01}, C_{02}, J_0]$	[1,2,3]	Individuals	[assumed,assumed,data]
$\Gamma(\theta)$	[0,1]	Individuals	assumed
$\Psi(\theta)$	[2,2]	Individuals	assumed
$\Omega(\theta)$	[4,4]	Individuals	data
Parameters			
Λ	$\mu_1 U(t) + \mu_2(C(t) + J(t))$	Individuals/day	-
m	0.04	Dimensionless	Assumed
β	0.001	1/day	Assumed
γ	0.58	Dimensionless	data
α	0.29	1/day	data
μ_1	0.16	1/day	data
μ_2	0.08	1/day	data

approximations in a space spanned by piecewise linear splines. An approximation to the solution of system (1) is obtained by calculating numerically the generalized time dependent Fourier coefficients of the approximate solutions corresponding to the spline representation. With these coefficients we can recover an approximation to the solution of the system. This approach provides a rigorous framework in which global existence and uniqueness of the solution along with convergence proofs can be given (see [5, 6, 8, 14, 28] for proofs).

5.1 Abstract evolution equation formulation

We use the notation of [8, 14]. Let $x(t)$ represent the state of the system (1) at time t, that is

$$x(t) = (C_1(t), C_2(t), J(t))^T,$$

and represent the function space state of the system due to the delay as

$$x_t(\tau) = x(t + \tau), \quad -2 \leq \tau \leq 0.$$

We define $Z \equiv \mathbb{R}^3 \times L^2(-2, 0; \mathbb{R}^3)$ as the infinite dimensional Hilbert space with norm

$$|(\eta, \phi)|_Z = \left(|\eta|^2 + \int_{-2}^{0} |\phi(\tau)|^2 d\tau \right)^{1/2},$$

where $(\eta, \phi) \in Z$ and L^2 is the space of square integrable functions, and inner product

$$\langle (\eta, \phi), (\zeta, \psi) \rangle_Z = \eta^T \zeta + \int_{-2}^{0} \phi(\tau)^T \psi(\tau) d\tau$$

for $(\eta, \phi), (\zeta, \psi) \in Z$.

Then the system (1) can be written as

$$\begin{aligned} \frac{dx(t)}{dt} &= L(x(t), x_t) + f(x(t)) + g \quad \text{for} \quad t_i < t \leq t_{i+1}, \\ (x(0), x_0) &= (\Phi(0), \Phi) \in Z, \end{aligned} \tag{10}$$

where $t > 0$ and $\Phi \in \mathcal{C}(-2, 0; \mathbb{R}^3)$ is the trajectory history function of the system defined on $[-2, 0]$.

In the model (10), g is the state independent part of the system, $L(x(t), x_t)$ is the linear part of the system, and $f(x(t))$ is the nonlinear part of the system. If we let $\delta_{-2}(\tau)$ be the Dirac delta 'density' (corresponding to a Heaviside distribution with a unit jump at $\tau = -2$), we have

$$g = \begin{bmatrix} mN\mu_1(1 - e^{-2\mu_2}) \\ 0 \\ mN\mu_1 e^{-2\mu_2} \end{bmatrix}$$

$$\begin{aligned} L(\eta, \phi) = &\begin{bmatrix} m(\mu_2 - \mu_1) - \mu_2 & m(\mu_2 - \mu_1) & m(\mu_2 - \mu_1) \\ \beta N & \beta N - \mu_2 & \beta N(1 - \gamma) \\ 0 & 0 & -\mu_2 \end{bmatrix} \eta \\ &+ me^{-2\mu_2}(\mu_2 - \mu_1) \begin{bmatrix} -1 & -1 & -1 \\ 0 & 0 & 0 \\ 1 & 1 & 1 \end{bmatrix} \int_{-2}^{0} \phi(\tau) \delta_{-2}(\tau) d\tau \end{aligned}$$

$$f(\eta) = \begin{bmatrix} 0 & 0 & 0 \\ -\beta[\eta_1 + 2\eta_2 + (2 - \gamma)\eta_3] & -\beta[\eta_2 + (2 - \gamma)\eta_3] & -\beta(1 - \gamma)\eta_3 \\ 0 & 0 & 0 \end{bmatrix} \eta.$$

With respect to the nonlinear terms in $f(\eta)$, a more realistic model requires that these terms be bounded in the limit (i.e., saturation should be considered in the nonlinear terms so that in the limit it is at least affine in x_1 or x_2 or x_3). For well posedness considerations the nonlinear terms can be replaced by a function such as:

$$\beta_i(x_i) = \begin{cases} 0 & x_i < 0 \\ \beta x_i & 0 \leq x_i \leq \bar{x}_i \\ \beta \bar{x}_i & \bar{x}_i < x_i \end{cases}$$

with $\bar{x_i} \in \mathbb{R}^+$ as finite upper bounds and $i = 1, 2, 3$. Then $f(\eta)$ can be replaced by

$$\tilde{f}(\eta) = \begin{bmatrix} 0 & 0 & 0 \\ -\beta_1(\eta_1) - 2\beta_2(\eta_2) - (2-\gamma)\beta_3(\eta_3) & -\beta_2(\eta_2) - (2-\gamma)\beta_3(\eta_3) & -(1-\gamma)\beta_3(\eta_3) \\ 0 & 0 & 0 \end{bmatrix} \eta,$$

which yields

$$\begin{aligned} \frac{dx(t)}{dt} &= L(x(t), x_t) + \tilde{f}(x(t)) + g \quad \text{for} \quad t_i < t \leq t_{i+1}, \\ (x(0), x_0) &= (\Phi(0), \Phi) \in Z. \end{aligned} \tag{11}$$

5.2 Abstract evolution equation implementation

We define a nonlinear operator $\mathcal{A} : \mathcal{D}(\mathcal{A}) \subset Z \to Z$ by

$$\mathcal{A}(\phi(0), \phi) = \left(L(\phi(0), \phi) + \tilde{f}(\phi(0)), \frac{d}{d\tau}\phi \right)$$

with domain defined as

$$\mathcal{D}(\mathcal{A}) = \{(\phi(0), \phi) \in Z | \phi \in H^1(-2, 0; \mathbb{R}^3)\}.$$

where neither the nonlinear operator $\mathcal{A}$ nor the domain $\mathcal{D}(\mathcal{A})$ depends on t. If we let $z(t) = (x(t), x_t) \in Z$, then the delay system (11) can be formulated as

$$\begin{aligned} \frac{dz(t)}{dt} &= \mathcal{A}z(t) + (g, 0) \\ z(0) &= z_0. \end{aligned} \tag{12}$$

Define Z^M to be the approximating piecewise linear spline [14, 15] subspace of Z, P^M as the orthogonal projection of Z onto Z^M, and $\mathcal{A}^M$ as the approximating operator of $\mathcal{A}$ given by $\mathcal{A}^M = P^M \mathcal{A} P^M$ (again, see [8, 14]). Then the system (12) can be approximated by the finite dimensional system

$$\begin{aligned} \frac{dz^M(t)}{dt} &= \mathcal{A}^M z^M(t) + P^M(g, 0) \\ z^M(0) &= P^M z_0. \end{aligned} \tag{13}$$

We define a basis and representation for Z^M. By partitioning the interval $[-2, 0]$

with $t_j^M = -j(2/M)$ for $j = 0, ..., M$, we can define a basis $\hat{\beta}^M$ by

$$\hat{\beta}^M = (\beta^M(0), \beta^M) \quad \text{where} \quad \beta^M = (e_0^M, e_1^M, ..., e_M^M) \otimes \mathbb{I}_3,$$

and an element in Z^M can be written as

$$z^M = \hat{\beta}^M \alpha^M = \sum_{j=0}^{M} (e_j^M(0), e_j^M) a_j^M,$$

with $a_j^M \in \mathbb{R}^M$ and the e_j^M's are piecewise linear functions with $e_j^M(t_i^M) = \delta_{ij}$ for $i, j = 0, ..., M$.

Define A_1^M as a matrix representation of $\mathcal{A}^M$ restricted to the subspace Z^M and let $w^M(t)$ and K^M be defined such that $z^M(t) = \hat{\beta}^M w^M(t)$ and $P^M(g, 0) = \hat{\beta}^M K$. Then, solving for $z^M(t)$ in the finite dimensional system (13) is equivalent to solving for $w^M(t)$ in the system

$$\begin{aligned} \frac{dw^M(t)}{dt} &= A^M w^M(t) + K^M \\ w^M(0) &= w_0^M, \end{aligned} \tag{14}$$

where $\hat{\beta}^M w_0^M = P^M z_0$. We remark that based on previous theory–see [5, 6, 28], having obtained w^M, the product $\hat{\beta}^M w^M(t)$ converges uniformly in t to the solution of (12).

In order to approximate $P^M(\eta, \phi)$ for any $(\eta, \phi) \in Z$, where $P^M(\eta, \phi)$ is the orthogonal projection of $(\eta, \phi) \in Z$ onto Z^M, assume $P^M(\eta, \phi) = \hat{\beta}^M u^M$ where $u^M \in \mathbb{R}^3$ then

$$0 = \langle \hat{\beta}^M u^M - (\eta, \phi), \hat{\beta}^M \rangle_Z$$

which implies that

$$\langle \hat{\beta}^M, \hat{\beta}^M \rangle u^M = \langle \hat{\beta}^M, (\eta, \phi) \rangle_Z. \tag{15}$$

The orthogonal projection P^M is uniquely determined by solving (15) for u^M and implies that

$$K^M = (\langle \hat{\beta}^M, \hat{\beta}^M \rangle_Z)^{-1} \langle \hat{\beta}^M, (g, 0) \rangle_Z$$

and

$$w_0^M = (\langle \hat{\beta}^M, \hat{\beta}^M \rangle_Z)^{-1} \langle \hat{\beta}^M, (x(0), x_0) \rangle_Z.$$

Similarly, in order to approximate $A^M \alpha^M$ for any $\alpha^M \in \mathbb{R}^3$, we observe that

$$\mathcal{A}^M \hat{\beta}^M \alpha^M = P^M(\mathcal{A} \hat{\beta}^M \alpha^M) = \hat{\beta}^M A_1^M \alpha^M$$

and

$$P^M(\mathcal{A} \hat{\beta}^M \alpha^M) = P^M(L(\beta^M(0)\alpha^M, \beta^M \alpha^M) + \tilde{f}(\beta^M(0)\alpha^M), \tfrac{d}{d\tau}(\beta^M \alpha^M)).$$

Thus

$$0 = \hat{\beta}^M A_1^M \alpha^M - P^M(L(\beta^M(0)\alpha^M, \beta^M\alpha^M) + \tilde{f}(\beta^M(0)\alpha^M), \tfrac{d}{d\tau}(\beta^M\alpha^M))$$

and

$$0 = \langle \hat{\beta}^M, \hat{\beta}^M A_1^M \alpha^M - (L(\beta^M(0)\alpha^M, \beta^M\alpha^M) + \tilde{f}(\beta^M(0)\alpha^M), \tfrac{d}{d\tau}(\beta^M\alpha^M)))\rangle_Z,$$

which implies that

$$\langle \hat{\beta}^M, \hat{\beta}^M\rangle_Z(A_1^M\alpha^M) = \langle \hat{\beta}^M, (L(\beta^M(0)\alpha^M, \beta^M\alpha^M) + \tilde{f}(\beta^M(0)\alpha^M), \frac{d}{d\tau}(\beta^M\alpha^M))\rangle_Z. \tag{16}$$

Therefore, $A_1^M\alpha^M$ is uniquely defined by solving (16) and implies that

$$A_1^M w^M(t) = (\langle \hat{\beta}^M, \hat{\beta}^M\rangle_Z)^{-1} Q^M w^M(t)$$

where

$$Q^M = \langle \beta^M(0), L(\beta^M(0), \beta^M) + \tilde{f}(\beta^M(0))\rangle + \langle \beta^M, \dot{\beta}^M\rangle.$$

5.3 Convergence of solutions

Before performing an inverse problem using the discrete event model with delay (1) one needs to know how many partitions M to take in the interval [-2, 0] so that the solutions of (13) are close to the solutions of (12)– we are guaranteed convergence as $M \to \infty$. In order to do this, we carried out simulations for the forward problem for increasing values of M with the parameter values presented in Table 2.

We used Matlab's *ode*45 to solve system (14) with $M = 12, 24, 48, 96$. In Figure 2 we present the solutions for each M value. Note that solutions corresponding to the $M = 24, 48, 96$ values are very close. However, these results coupled with the computational times required in solving the system on the time interval $t = [0, 100]$ (see Table 3) suggest that any M between 24 and 48 appears to be a reasonable choice for this system. We remark that the computational time increases by a factor of 12 when we increase the partitions from $M = 48$ to $M = 96$. As a result of these investigations, we chose $M = 30$ for our continuing considerations.

Table 3: Computational times required to solve the discrete event model with delay (1) for increasing number M of partitions using oncology unit parameters.

M (partitions)	Time (s)
12	1.99
24	18.17
48	194.44
96	2,402.10

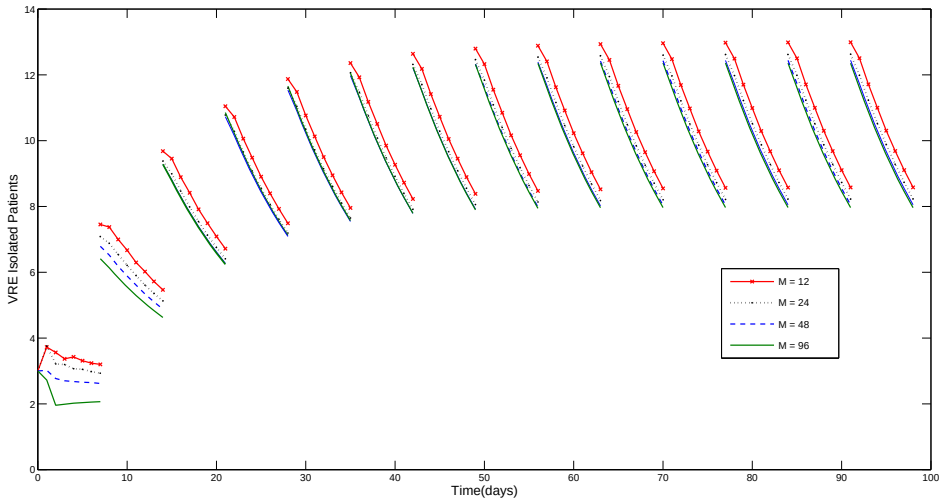


Figure 2: Solutions of the discrete event model (1) with delay for increasing M using the oncology unit parameters

6 Inverse Problem

6.1 Least squares theory

We next consider a least square formulation of a generic inverse problem for a vector θ dependent system

$$\begin{aligned} \frac{dx(t)}{dt} &= g(t, x(t;\theta), \theta) \\ x(t_0) &= x_0, \end{aligned} \tag{17}$$

with parameter vector $\theta \in \mathbb{R}^p$, $x(t) = (x_1(t), ..., x_N(t))^T \in \mathbb{R}^N$, and an observational process $y(t_j) = Cx(t_j;\theta) \in \mathbb{R}^m$ for $j = 1, ..., n$, where C is an $m \times N$ matrix. The

mathematical model is assumed to be well-posed (i.e., existence of a unique solution that depends smoothly on the parameters and initial data).

Let Y_j, for $j = 1, ..., n$, be longitudinal data observations corresponding to the experimental data of the observational process. Since in general Y_j is not assumed to be free of error (i.e., error in the data collection process), Y_j will not be $y(t_j)$. We can thus envision experimental data as generally consisting of observations from a "perfect model" plus an error component represented by the statistical model

$$Y_j = f(t_j; \theta_0) + \mathcal{E}_j \qquad \text{for} \quad j = 1, .., n, \tag{18}$$

where θ_0 corresponds to the "true" parameter that would generate error free observations $\{Y_j\}$. The function $f(t_j, \theta)$ corresponds to the observation process for model (17) and depends on the parameters θ in a nonlinear fashion.

The $\mathcal{E}_j$'s are random variables and we make the following standard assumptions on our statistical model: (i) The measurement errors $\mathcal{E}_j$ for $j = 1, .., n$ have mean zero, i.e., $E(\mathcal{E}_j) = 0$; (ii) The measurement errors $\mathcal{E}_j$ for $j = 1, .., n$ have the same variance, i.e., $var(\mathcal{E}_j) = \sigma_0^2 < \infty$, and are independent identically distributed (*iid*) random variables for all t_j.

If the error distribution is unknown, an ordinary least squares (OLS) optimization procedure is often employed [9]. This method yields the estimator

$$\theta_{OLS} = \theta_{OLS}^n = \arg\min_{\theta \in \Theta} \sum_{j=1}^{n} |Y_j - f(t_j, \theta)|^2. \tag{19}$$

This corresponds to solving for θ in

$$\sum_{j=1}^{n} [Y_j - f(t_j, \theta)] \nabla f(t_j, \theta) = 0.$$

It is of interest to know the distribution of θ_{OLS} and for this we have the asymptotic theory (for details see [9, 24, 33]) which yields that as $n \to \infty$

$$\theta_{OLS} = \theta_{OLS}^n \sim N_p(\theta_0, \Sigma_0^n), \tag{20}$$

where the covariance matrix Σ_0^n is defined by

$$\Sigma_0^n \equiv \sigma_0^2 [n\Omega_0]^{-1}$$

and

$$\Omega_0 \equiv \lim_{n \to \infty} \frac{1}{n} \chi^n(\theta_0)^T \chi^n(\theta_0).$$

Here $\chi^n(\theta) = \{\chi_{jk}\}$ is the sensitivity matrix defined by

$$\chi_{jk}(\theta) = \frac{\partial f(t_j, \theta)}{\partial \theta_k} \quad j = 1, ..., n \quad \text{and} \quad k = 1, ..., p.$$

Given $\hat{\theta}_{OLS}$, the estimate corresponding to a specific realization $\{y_j\}$ of $\{Y_j\}$, the error variance σ_0^2 is approximated by

$$\hat{\sigma}^2_{OLS} = \frac{1}{n-p}\sum_{j=1}^{n} |Y_j - f(t_j, \hat{\theta}_{OLS})|^2 \tag{21}$$

which is the bias adjusted estimate for σ_0^2. The covariance matrix Σ_0^n is approximated by

$$\hat{\Sigma}^n_{OLS} = \hat{\sigma}^2_{OLS}[\chi^T(\hat{\theta}_{OLS})\chi(\hat{\theta}_{OLS})]^{-1}. \tag{22}$$

Therefore as $n \to \infty$

$$\theta_{OLS} \sim \mathcal{N}_p(\theta_0, \Sigma_0^n) \approx \mathcal{N}_p(\hat{\theta}_{OLS}, \hat{\Sigma}^n_{OLS}). \tag{23}$$

If the error distribution is unknown and the assumption of constant variance of the error in the longitudinal data does not hold, we need to formulate a new statistical model to take into consideration the non-constant error variability. In this case a generalized least square (GLS) optimization procedure may be more appropriate. If we can assume that the size of the error depends on the size of the observed quantity, the statistical model (i.e, a relative error model) is given by

$$Y_j = f(t_j, \theta_0)(1 + \mathcal{E}_j) \qquad \text{for} \quad j = 1, .., n, \tag{24}$$

where under assumptions (i)-(ii) we have $Y_j \sim \mathcal{N}(f(t_j, \theta_0), \sigma_0^2 f^2(t_j, \theta_0))$. In this case, GLS can be viewed as minimizing the distance between the data and the model while taking into account unequal quality of the observations. The GLS method defines the estimator $\hat{\theta}_{GLS}$ as the solution of the *normal equations*

$$\sum_{j=1}^{n} f^{-2}(t_j, \theta_{GLS})[Y_j - f(t_j, \theta_{GLS})]\nabla f(t_j, \theta_{GLS}) = 0. \tag{25}$$

For motivation underlying this definition see [9, 24]. The idea is to assign to each model dependent observation a weight that reflects the uncertainty in that observation. From the corresponding asymptotic theory we have as $n \to \infty$

$$\theta_{GLS} = \theta^n_{GLS} \sim \mathcal{N}_p(\theta_0, \Sigma_0^n) \tag{26}$$

where

$$\Sigma_0^n \approx \sigma_0^2[F^T(\theta_0)W(\theta_0)F(\theta_0)]^{-1}$$

with

$$F(\theta) = \begin{bmatrix} \frac{\partial f(t_1,\theta)}{\partial \theta_1} & \cdots & \frac{\partial f(t_1,\theta)}{\partial \theta_p} \\ \vdots & & \vdots \\ \frac{\partial f(t_n,\theta)}{\partial \theta_1} & \cdots & \frac{\partial f(t_n,\theta)}{\partial \theta_p} \end{bmatrix}$$

and $W^{-1}(\theta) = diag(f^2(t_1,\theta),...,(f^2(t_n,\theta))$. For the estimates we have the covariance matrix approximation ($\hat{\theta}_{GLS}$ is the estimate corresponding to a realization of $\{Y_j\}$)

$$\Sigma_0^n \approx \hat{\Sigma}_{GLS}^n = \hat{\sigma}_{GLS}^2[F^T(\hat{\theta}_{GLS})W(\hat{\theta}_{GLS})F(\hat{\theta}_{GLS})]^{-1}, \tag{27}$$

and the error variance approximation

$$\hat{\sigma}_{GLS}^2 = \frac{1}{n-p}\sum_{j=1}^{n}\frac{1}{f^2(t_j,\hat{\theta}_{GLS})}|Y_j - f(t_j,\hat{\theta}_{GLS})|^2. \tag{28}$$

Therefore we approximate in the asymptotic theory by

$$\theta_{GLS} \sim \mathcal{N}_p(\theta_0,\Sigma_0^n) \approx \mathcal{N}_p(\hat{\theta}_{GLS},\hat{\Sigma}_{GLS}^n). \tag{29}$$

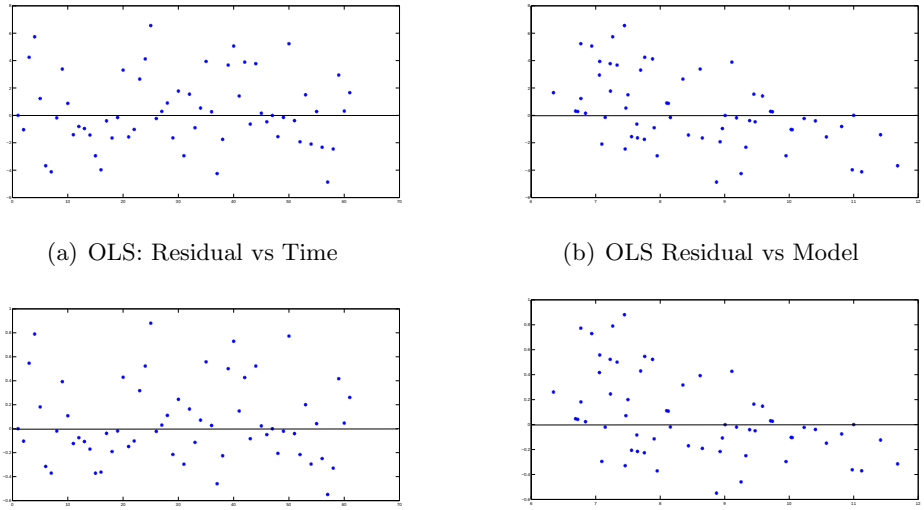
We can also calculate the standard errors for $\hat{\theta}_{GLS}$ by taking the square roots of the diagonal elements of the covariance matrix $\hat{\Sigma}_{GLS}^n$.

6.2 Inverse problem results

We present results of estimating $\theta = (\beta)$ and $\theta = (m,\beta)$ using the model (1). We demonstrate the numerical and statistical capabilities of our model and associated inverse problem algorithms with simulated "data" in Section 8.

As we mentioned before, the VRE surveillance data does not report the number of patients in isolation during weekends and holidays. Not surprising, when trying to fit the model (1) to the data, we found that there were in many periods additional observations missing that did not correspond to weekends and holidays. However, we identified a period of about three months (January 17, 2006 to April 13, 2006) that only had weekends as missing values and used these to carry out the inverse problems. Since our model is continuous through weekends, in order to carry out the fitting we omitted any weekend observations from the cost functional.

Residuals (see [9] for a discussion of the use of residual plots in post inverse problem analysis) and the best fit-to-data as a result of estimating $\theta = (\beta)$ are depicted in Figure 3 and Figure 4. Results from estimating $\theta = (m,\beta)$ are given in Figure 5 and Figure 6. Overall, from the residual analysis we can conclude that whether we use OLS or GLS, the errors are independent (residuals vs time are random). On the other hand, the residuals versus model plot for OLS compared to the residuals/model versus model for GLS have the same pattern indicating no difference in whether we use an absolute error model or a relative error model. Given the wide variability in the VRE data, we are led to suspect that the apparent discrepancy in the statistical model may be due to *model error* rather than measurement error.



(a) OLS: Residual vs Time

(b) OLS Residual vs Model

(c) GLS: Residual/Model vs Time

(d) GLS: Residual/Model vs Model

Figure 3: Residual analysis for the OLS and GLS optimization with model (1) as a result of estimating $\theta = (\beta)$ using oncology unit surveillance data.

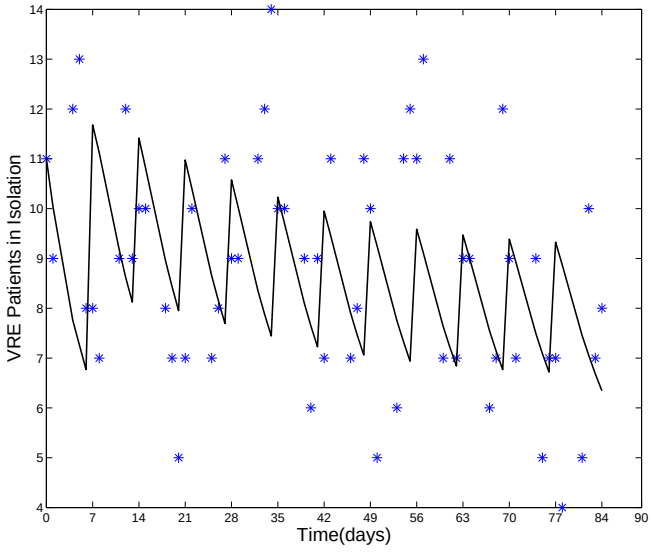
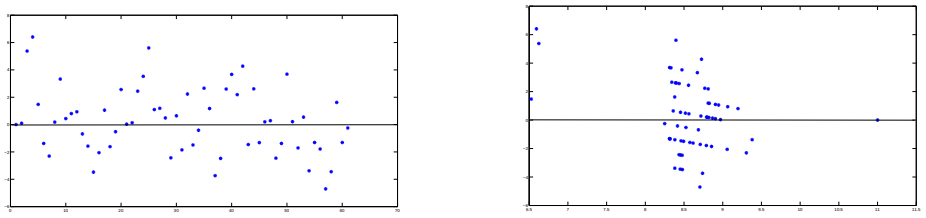
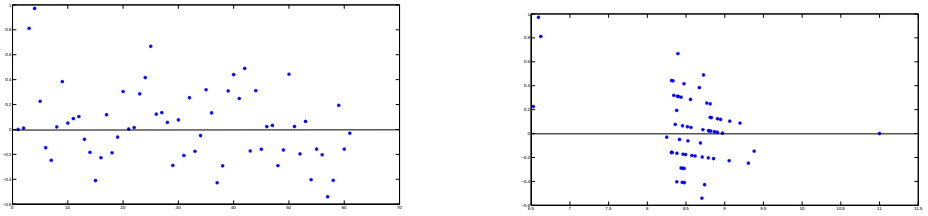


Figure 4: Best fit model solutions (model (1)) to oncology unit surveillance data via OLS optimization, $\hat{\beta} = 0.0039$. At each jump, data is fit using the model value after isolation.



(a) OLS: Residual vs Time

(b) OLS Residual vs Model



(c) GLS: Residual/Model vs Time

(d) GLS: Residual/Model vs Model

Figure 5: Residual analysis for the OLS and GLS optimization as a result of estimating $\theta = (m, \beta)$ using oncology unit surveillance data.

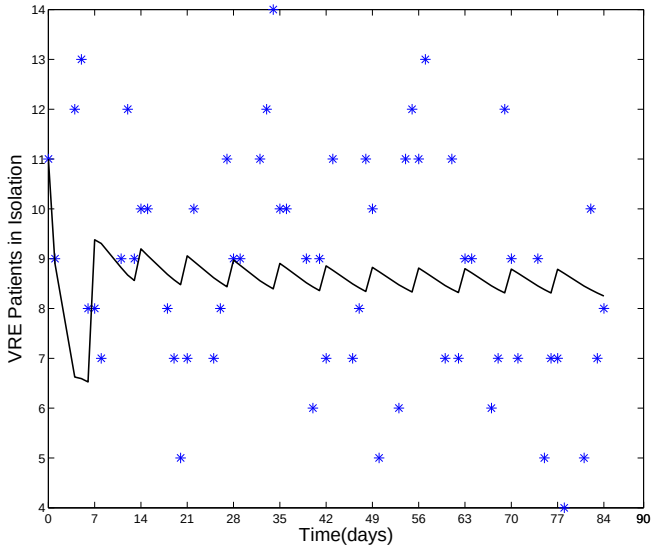


Figure 6: Best fit model solutions (model (1)) to oncology unit surveillance data via OLS optimization, $(\hat{m}, \hat{\beta}) = (0.1332, 0.008)$. At each jump, data is fit using the model value after isolation.

7 Model refinement

The inverse problem results from the previous section using the model (1) suggests that the model fit does not agree particularly well with the underlying process. Therefore, we refined the model, allowing more realistic details in the model, and compared it again to the data to investigate if there were possible improvements in the model fit.

Details that we included in the model are based on a faithful description of hospital routine for patients that are VRE colonized on admission. The epidemiology laboratory is closed on weekends and this results in two consequences. First, pending test-results from patients admitted on a Thursday or a Friday will be back by Monday or Tuesday. Second, swab-tests taken on patients admitted on a Saturday and a Sunday will be sent to the epidemiology laboratory on Monday, then these patients will be isolated by Wednesday. For simplicity, we focused on the first detail to see if accurate rendering of these details in the model provides any improvement in the model fit.

We assume that for patients that are admitted on Thursdays and Fridays, the test-results are back on Tuesdays. These patients will be moved into isolation by Tuesday night. As a result, we also have a jump discontinuity every Tuesday. If we let $\hat{t}_j$ be a Tuesday and $\hat{t}_{j+1}$ be the next Tuesday then

$$C_1(\hat{t}_{j+1}^+) \;=\; C_1(\hat{t}_{j+1}^-) - C_1(\hat{t}_{j+1}-4)e^{-4\mu_2} \tag{30}$$

represents the number of patients in C_1 after isolation on Tuesday. This is basically the number of patients in compartment C_1 before isolation minus the number of patients that were isolated at time $\hat{t}_{j+1}$. Hence, $C_1(\hat{t}_{j+1}-4)$ represents the number of patients in C_1 on a Friday (this includes the ones that where admitted on a Thursday and have not been discharged by Friday) and $e^{-4\mu_2}$ is the fraction of those $C_1(\hat{t}_{j+1}-4)$ that were not discharged over a period of 4 days before isolation (this follows the same derivation as in (5.4)). Consequently, this jump discontinuity in C_1 influences a positive jump in J defined as

$$J(\hat{t}_{j+1}^+) \;=\; J(\hat{t}_{j+1}^-) + C_1(\hat{t}_{j+1}-4)e^{-4\mu_2}, \tag{31}$$

where $J(\hat{t}_{j+1}^+)$ represent the total number of patients in isolation after that the isolation on Tuesday takes place. The dynamics for compartment C_1 at time t are modeled by

$$\begin{aligned}
\frac{dC_1(t)}{dt} &= m\{\mu_1 N + (\mu_2-\mu_1)[C_1(t)+C_2(t)+J(t)]\} \\
&- me^{-2\mu_2}\{\mu_1 N + (\mu_2-\mu_1)[C_1(t-2)+C_2(t-2)+J(t-2)]\} \\
&- \mu_2 C_1(t) \quad \text{for } \hat{t}_j < t < t_{Sat}, \qquad (32)\\
\frac{dC_1(t)}{dt} &= m\{\mu_1 N + (\mu_2-\mu_1)[C_1(t)+C_2(t)+J(t)]\} \\
&- \mu_2 C_1(t) \quad \text{for } t_F < t \le \hat{t}_{j+1}, \qquad (33)
\end{aligned}$$

with t_F as day Friday and t_{Sat} as day Saturday. Equation (32) models the rate of

change of C_1's from Wednesday through Friday in which isolation takes place by the corresponding rate. On the other hand, Equation (33) models the rate of change of C_1's from Saturday through Tuesday in which isolation is not employed. Tuesday is included on the interval because it corresponds to the number of C_1's on Tuesday before isolation takes place. Finally, the complete model that includes the new detail is given by

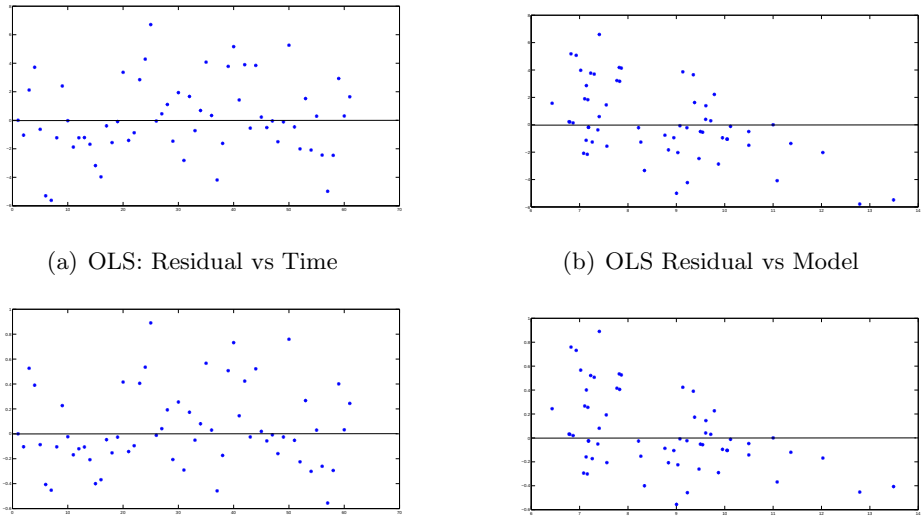
$$\begin{aligned}
\frac{dC_1(t)}{dt} &= m\{\mu_1 N + (\mu_2-\mu_1)[C_1(t)+C_2(t)+J(t)]\} \\
&- me^{-2\mu_2}\{\mu_1 N + (\mu_2-\mu_1)[C_1(t-2)+C_2(t-2)+J(t-2)]\} \\
&- \mu_2 C_1(t) \quad \text{for } \hat{t}_j < t < t_{Sat}, \\
\frac{dC_1(t)}{dt} &= m\{\mu_1 N + (\mu_2-\mu_1)[C_1(t)+C_2(t)+J(t)]\} \\
&- \mu_2 C_1(t) \quad \text{for } t_F < t \le \hat{t}_{j+1}, \\
C_1(\hat{t}_{j+1}^+) &= C_1(\hat{t}_{j+1}^-) - C_1(\hat{t}_{j+1}-4)e^{-4\mu_2}, \\
\frac{dC_2(t)}{dt} &= \beta\{N-[C_1(t)+C_2(t)+J(t)]\}[C_1(t)+C_2(t)+(1-\gamma)J(t)] \\
&- \mu_2 C_2(t), \quad \text{for } t_i < t \le t_{i+1}, \\
C_2(t_{i+1}^+) &= C_2(t_{i+1}^-) - C_2(t_{i+1}-2)e^{-2\mu_2}, \\
\frac{dJ(t)}{dt} &= me^{-2\mu_2}\{\mu_1 N + (\mu_2-\mu_1)[C_1(t-2)+C_2(t-2)+J(t-2)]\} \\
&- \mu_2 J(t), \quad \text{for } \hat{t}_{j+1} < t < t_{Sat}, \\
\frac{dJ(t)}{dt} &= -\mu_2 J(t), \quad \text{for } t_F < t < \hat{t}_{j+1}, \\
J(\hat{t}_{j+1}^+) &= J(\hat{t}_{j+1}^-) + C_1(\hat{t}_{j+1}-4)e^{-4\mu_2}, \\
J(t_{i+1}^+) &= J(t_{i+1}^-) + C_2(t_{i+1}-2)e^{-2\mu_2}. \qquad (34)
\end{aligned}$$

with t_F as day Friday, t_{Sat} as day Saturday, $\hat{t}_j$ as isolation-day on Tuesday, t_i as isolation-day on Thursday. Initial conditions are: $C_1(0) = C_{01}$, $C_2(0) = C_{02}$, $J(0) = J_0$, and a trajectory of the solution in the past: $C_1(\theta) = \Gamma(\theta)$, $C_2(\theta) = \Psi(\theta)$, $J(\theta) = \Omega(\theta)$ for $\theta \in [-2, 0)$.

7.1 Inverse problem results

In this section we present the results of estimating $\theta = (\beta)$ using the refined model (34) with the surveillance data. We also verify the numerical accuracy of the computations for the refined model. Section 8 contains details on numerical validation as well as model comparison details.

Figure 7 depicts the residual analysis and Figure 8 depicts the best fit to data for model (34) . The results indicate that there is not significant improvement in the model fit to the data. That is, the additional detail in the model corresponding to jumps on Tuesdays does not have a significant effect in the fit to the data.



(a) OLS: Residual vs Time

(b) OLS Residual vs Model

(c) GLS: Residual/Model vs Time

(d) GLS; Residual/Model vs Model

Figure 7: Refined model: Residual analysis for the OLS and GLS optimization with model (34) as a result of estimating $\theta = (\beta)$ using oncology unit surveillance data.

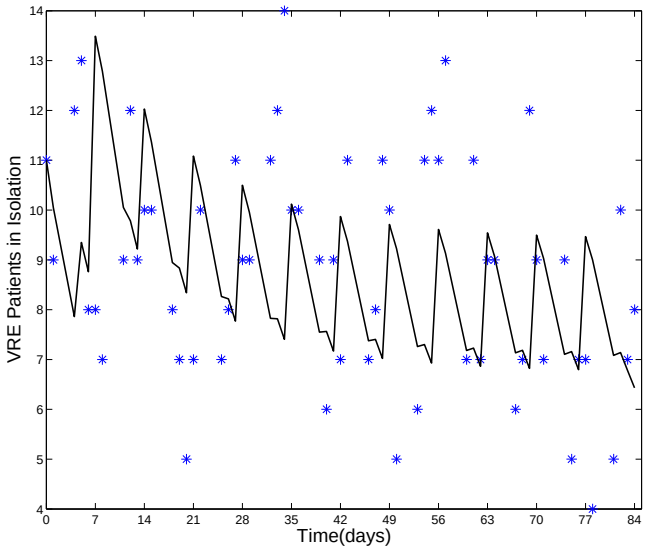


Figure 8: Refined model: Best fit model solutions to oncology unit surveillance data via OLS optimization with model (34), $\hat{\beta} = 0.0039$. Note jumps every 5 days corresponding to every Tuesdays and jumps every 7 days corresponding to Thursdays. At each jump, data is fit using the model value after isolation.

8 Models comparison and algorithm analysis

We next report on comparison of model (1) with model (34) as well as validate the numerical accuracy of these models when carrying out an inverse problem.

In order to compare both models, we simulated a solution with the parameters values recorded in Table 4. Figure 9 contains a plot of the forward solutions of the models in comparison to the data. The plots indicate that *relative to the data* the dynamics of model (1) in comparison to model (34) are essentially the same. In the first 14 days we see a little difference but after that there is no qualitative difference except for the Tuesdays' jump in model (34). We can conclude that with the addition in model (34) of more details to model (1) there appears to be no significant improvement over model (1) fits to the surveillance data.

In order to test the computational efficacy of use of the models in inverse problem calculations, we added noise (constant variance error) to the forward solution and carried out an inverse problem using the noise-added solution as synthetic data to attempt to recover the original parameters. In other words, realizations of synthetic data $\{y_j\}$ for $j = 1, ..., n$, are constructed by adding variability to the model solution, $f(t_j, \theta_0) = J(t_j, \theta_0)$. The statistical model that captures the variability is

$$Y_j = f(t_j, \theta_0) + \sigma Z_j \tag{35}$$

where Z_j is a standard normal variable (i.e., $Z_j \sim \mathcal{N}(0, 1)$) and σ^2 is the constant variance. The magnitude of σ determines the amount of noise added.

We conducted the inverse problems to estimate $\theta = (\beta)$ and $\theta = (m, \beta)$ via ordinary least squares (OLS) with different noise levels: $\sigma = 0, 0.10, 0.30, 0.50$ and 0.70. In Tables 5 and 6 we summarize the results for the estimation of $\theta = (\beta)$ and $\theta = (m, \beta)$ corresponding to model (1) and model (34). Fitting results are presented in Figures 10 and 11 for model (1), and Figures 12 and 13 for model (34). We can conclude that the estimation procedure performed adequately with each model when using noisy synthetic data.

Table 4: Parameters values used in the forward type problem to compare models

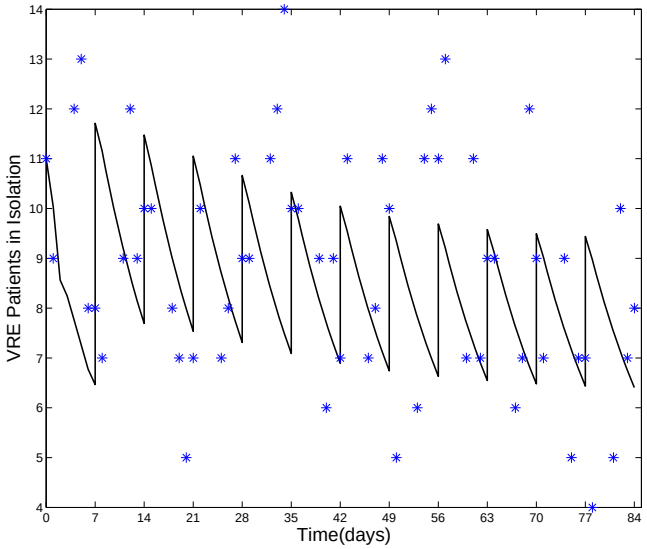
Initial Conditions	Units	Oncology Unit Values (N=37)
$x(0)$	Individuals	[2;4;11]
x_0	Individuals	[4,2;5,3;9,10]
Parameters		
Λ	Individuals/day	$0.16U(t) + 0.08(C(t) + J(t))$
m	Dimensionless	0.4
β	1/day	0.0039
γ	Dimensionless	0.58
α	1/day	0.29
μ_1	1/day	0.16
μ_2	1/day	0.08

Table 5: OLS optimization testing using Model (1) for parameter subsets $\theta = (\beta)$ and $\theta = (m, \beta)$. The model was fit to generated data with $\sigma = 0, 0.1, 0.3, 0.5, 0.7$.

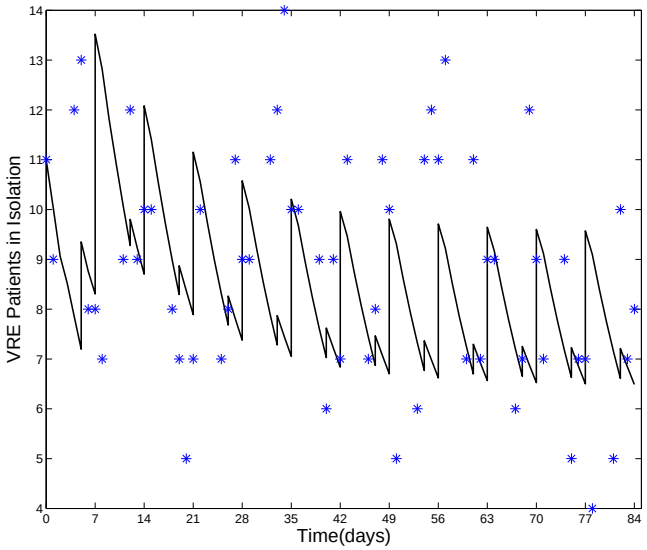
σ	0	0.1	0.3	0.5	0.7
m	-	-	-	-	-
β	0.0039	0.0039	0.0040	0.0041	0.0041
m	0.04	0.0392	0.0386	0.0364	0.0334
β	0.0039	0.0040	0.0040	0.0042	0.0043

Table 6: OLS optimization testing using Model (34) for parameter subsets $\theta = (\beta)$ and $\theta = (m, \beta)$. The model was fit to generate data with $\sigma = 0, 0.1, 0.3, 0.5, 0.7$.

σ	0	0.1	0.3	0.5	0.7
m	-	-	-	-	-
β	0.0039	0.0039	0.0040	0.0040	0.0041
m	0.04	0.0404	0.0407	0.0424	0.0449
β	0.0039	0.0039	0.0040	0.0040	0.0040

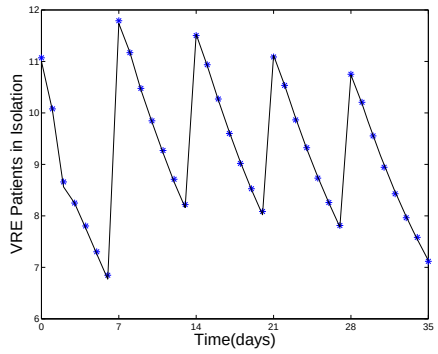


(a) Model (1) solution using forward type problem in comparison to the data. Note jumps every 7 days corresponding to Thursdays. Both values at the jump are plotted.

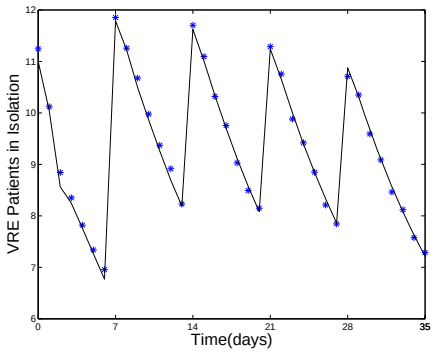


(b) Model (34) solution using forward type problem in comparison to the data. Note jumps every 5 days corresponding to Tuesdays and jumps every 7 days corresponding to Thursdays. Both values at the jumps are plotted.

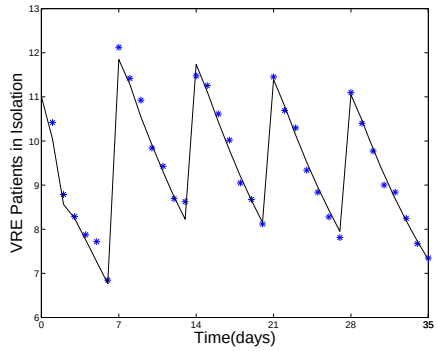
Figure 9: Solutions of the models using forward type problem in comparison to the oncology unit surveillance data.



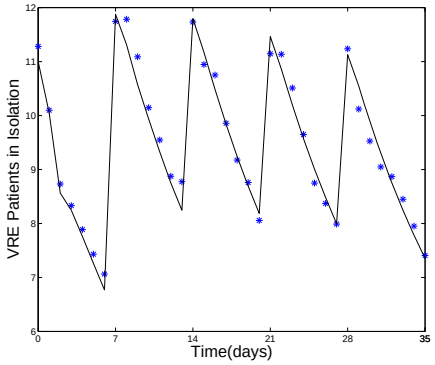
(a) Level of noise: σ=0.10



(b) Level of noise: σ=0.30

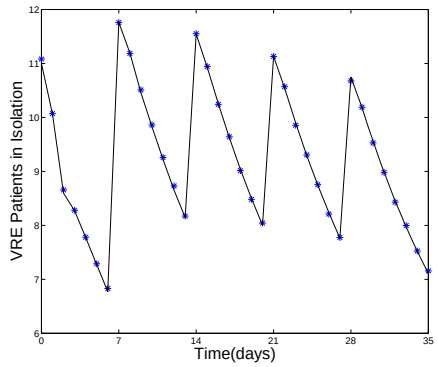


(c) Level of noise: σ=0.50

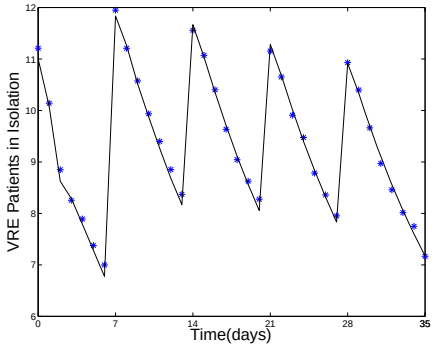


(d) Level of noise: σ=0.70

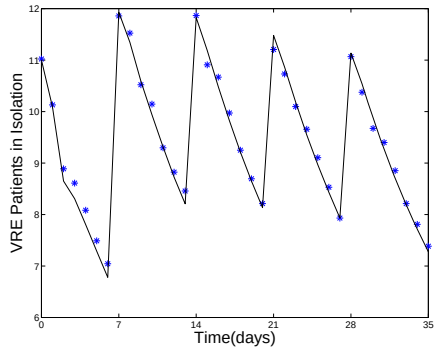
Figure 10: Model (1) fit to the synthetic data using OLS optimization procedure to estimate $\theta = (\beta)$.



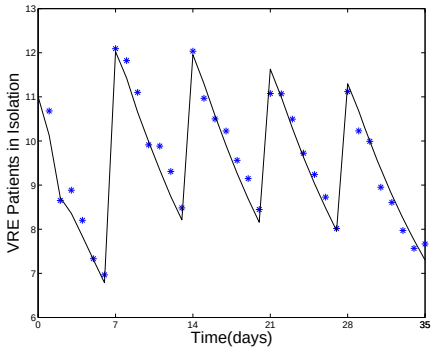
(a) Level of noise: σ=0.10



(b) Level of noise: σ=0.30

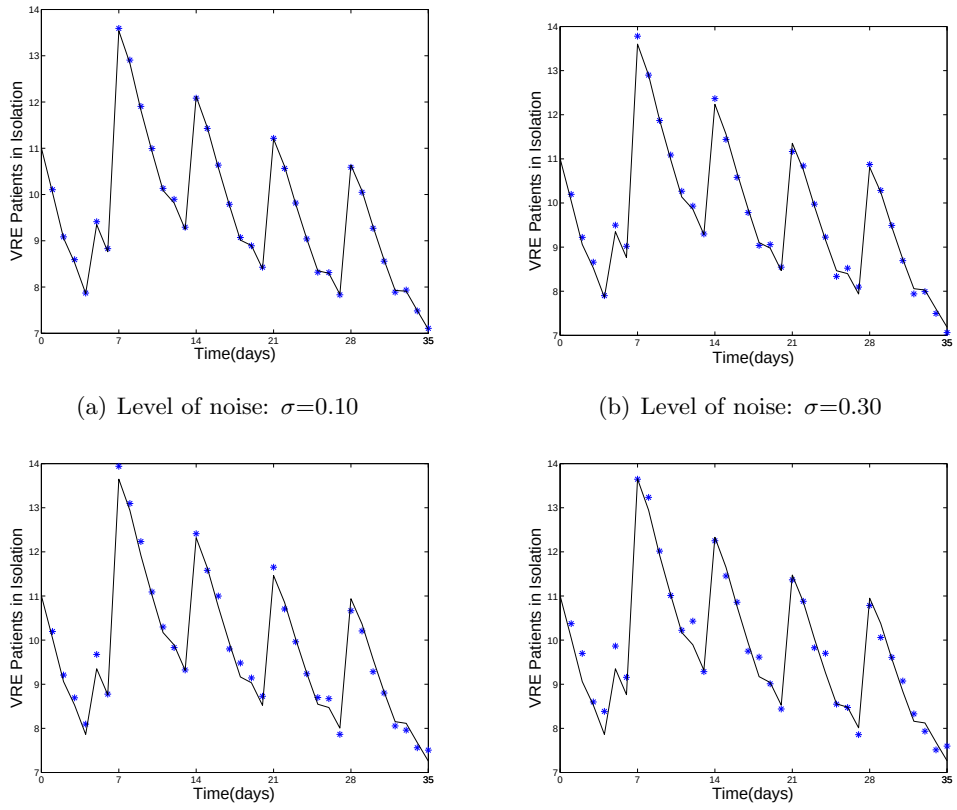


(c) Level of noise: σ=0.50



(d) Level of noise: σ=0.70

Figure 11: Model (1) fit to the synthetic data using OLS optimization procedure to estimate $\theta = (m, \beta)$.



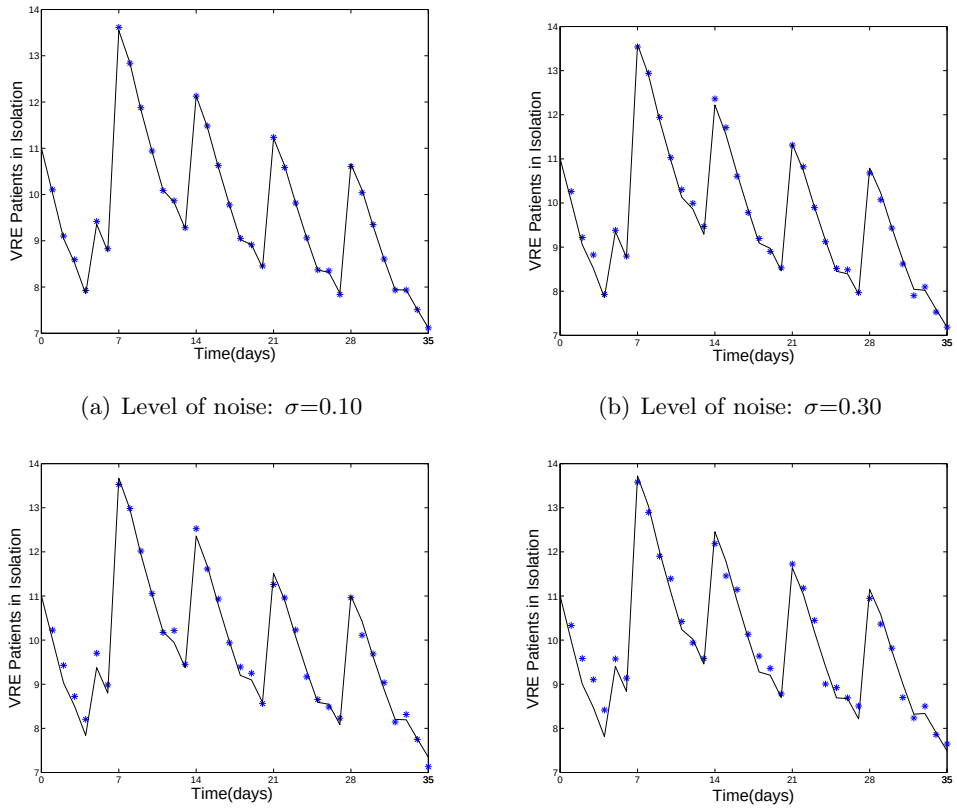
(a) Level of noise: σ=0.10

(b) Level of noise: σ=0.30

(c) Level of noise: σ=0.50

(d) Level of noise: σ=0.70

Figure 12: Model (34) fit to the synthetic data using OLS optimization procedure to estimate $\theta = (\beta)$.



(a) Level of noise: σ=0.10

(b) Level of noise: σ=0.30

(c) Level of noise: σ=0.50

(d) Level of noise: σ=0.70

Figure 13: Model (34) fit to the synthetic data using OLS optimization procedure to estimate $\theta = (m, \beta)$

9 Conclusions

We have introduced a discrete event VRE model with delay that incorporates specific details with respect to the isolation procedure employed to patients in a hospital unit. We attempted to estimate some of the epidemiological parameters such as the transmission rate (β) and the fraction (m) of patients VRE colonized on admission. Results suggested that there was little success in the model fits to the data, especially when trying to estimate $\theta = (m, \beta)$. We followed with a model refinement that includes additional detail to investigate whether an improvement in the model fits to the data could be achieved. Results revealed no improvement in the model fit to the data. To ensure that our inverse problem calculations were not the source of difficulty, we used simulated data (produced by the model with added noise) to validate our methodology and our ability to successfully estimate parameters in the model. Thus we demonstrated that if we have quality data for which the model is a reasonable approximation, we can successfully carry out the inverse problem, even with very noisy data.

We conclude that the VRE surveillance data appears to be very irregular as it does not seem to follow any standard process and contains an extemely high level of variability. One reason that the data has little to do with the process could be due to the fact that there is not a true parameter θ_0 in the statistical model, $Y_j = f(t_j, \theta_0) + \mathcal{E}_j$, that can generate the data we have from this hospital unit. The assumption of existence of such a θ_0 is an essential foundation of much of the statistical and mathematical methodology for inverse problems (see [9]). Another possible reason could be that it is likely that the underlying assumption for statistical model should be modified to $Y_j = f(t_j, \theta_0) + g(t_j, \theta_0)\mathcal{E}_j$, where we do not know $g(t_j, \theta)$. Another (more likely we believe) possibility is that there is no underlying model $f(t_j, \theta_0)$ that describes this data. In other words, this data is completely irregular due to inherent irregularities under data reporting. Thus we suspect that the quality of the data is not sufficient for model development. It is therefore, in the terminology introduced earlier, a prime example of "cold data" which is not adequate for model development and validation.

The models developed here involve a data collection process as described to us by the health workers. Thus we suggest that there are irregularities in reporting or in their descriptions of what they actually do. This claim is supported in Section 3.5 where we described inconsistencies in the data reporting. Any future efforts on model development would require a much more careful design and implementation of the data collection process.

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